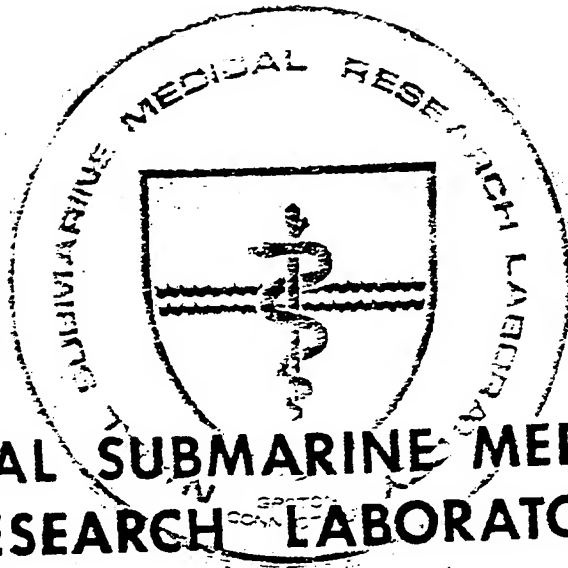


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REPORT NUMBER 803

Transthoracic Impedance Cardiography:
A Survey

Best Available Copy by

James Saklad, M.D.

Bureau of Medicine and Surgery, Navy Department
Research Work Unit M4386.02-7060.06

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Reviewed and Approved by:

Charles F. Gell, M.D., D.Sc.(Med)
Scientific Director
NavSubMedRschLab

Approved and Released by:

R. L. Sphar, CDR MC USN
Officer in Charge
NavSubMedRschLab

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Transthoracic Impedance Cardiography: A Survey

by

James Saklad

INTRODUCTION

Since the earliest times, practitioners of medicine have sought to learn more about the patients in their charge, and the afflictions which beset them, by means of methods least disturbing to the individual being investigated as possible. The ancient Chinese examined the pulse--in great detail, for hours--and a carved ivory "Doctor's Lady", whereon the afflicted woman pointed out her ills and described her pains, since actually handling the sick person was forbidden--certainly the ultimate in "noninvasive monitoring".

With the passage of time, the arts of physical diagnosis became developed to an exquisite degree: there are physicians today who can grade murmurs and estimate splitting of heart sounds accurately by touch. But as it became possible to put things into patients with relative safety and even impunity, ranging from the surgeon's gloved hand to cardiac pacemakers to biopsy needles to flow-directed intracardiac probes to selected coronary artery catheters to electromagnetic flow-probes to implantable strain-gages, medicine has come to rely more and more upon these gadgets.

But with more technological sophistication and more precise, and occasionally even more accurate, physiological measurements came greater risk to the patient, increased morbidity, and even mortality from what ought to be nearly harmless diagnostic procedures. More and more in recent years the attention of the medical and bioengineering community

has turned to methods of investigation which do less to the patient relative to what they do for the patient.

My interests here are particularly with the monitoring of the heart and its various parameters of function. The first of the good noninvasive cardiac measurement devices has been available for nearly all of this century, widely available for over 30 years, and nearly universal for 15 years--the electrocardiograph. With non-critical electrodes which are simple to attach and easy to maintain, it monitors the electrical activity of the heart in a continuous, beat-by-beat fashion; with suitable modifications, it is completely portable, to the point where even a SCUBA diver at several hundred feet depth, or a free-falling sky-diver can be monitored easily. But by its nature it is limited in the parameters it measures. It says nothing about cardiac output, myocardial contractility, cardiac "reserve", whether the individual is in or is approaching pulmonary edema, et cetera.

These are extremely important parameters to study for those who must understand the physiological changes of activity, of abnormal environments, of acute illnesses. Ideally, we would like to monitor these mechanical parameters as simply and as safely as we can the electrical parameters with an EKG. Direct measurement of myocardial contractility requires a strain-gage implanted directly onto the myocardium. We frown on this as being somewhat too invasive a technique for our purposes. This parameter can be indirectly monitored by measuring the intraventricular pressure changes of isometric ventricular contraction, and measuring the time interval from electrical initiation (the QRS complex of the EKG) to the maximum of the pressure derivative $\frac{dp}{dt}$. This still requires an intra-

ventricular catheter, but it's a little safer. Cardiac "reserve", and impending cardiac failure, can be measured with some accuracy by two common methods: radiographically, where heart size and shape tells the expert some useful information and fluid accumulations in the chest are visible when large, and barometrically, by placing a flow-directed catheter in the wedge position in a pulmonary artery and effectively determining left atrial pressure. The first is not particularly accurate or sensitive and is relatively slow and expensive, while the second is invasive and subject to all the inaccuracies and trouble of any catheter pressure measurement system.

Cardiac Output: "Standard" Techniques.

Cardiac output has been measured in a variety of ways¹⁸ over the years. Perhaps best, in the sense of having the clearest theoretical justification, and most accurate results, is the electromagnetic flowmeter. This is also the most invasive, requiring thoracotomy and stripping of part of the aorta. (I neglect the method of severing the aorta at the root and installing a direct flowmeter in series as this is impractical in humans, although useful sometimes in animal studies.) Heisenberg, it has been said, has done a remarkable service for the principle of objectivity in the observational sciences. We are compelled to wonder just what do thoracotomy, general anesthesia, surgical manipulation, and presence of the probe within the chest do to the cardiac output one hopes to measure?

The pressure-pulse contour methods have the advantage over some we shall discuss of providing, like the E-M flowmeter, beat-by-beat data: with a pressure probe in the ascending aorta we obtain instantaneous reading of beat-by-beat pressure, and can estimate the stroke volume for each beat by electronic analysis of the down-stroke (aortic-empty-

ing) phase of each beat. The theory behind this method, however, assumes certain elastic properties for the aorta and downstream vasculature, which properties unfortunately vary from individual to individual, and even over time within the same person. Further, shunts involving the systemic vasculature, or regurgitant disease of the aortic valve, will produce erroneous or biased data. Related to this method is the pressure-gradient technique, which suffers from fewer faults: if simultaneous lateral pressures are measured at two points in the proximal aorta, one a few centimeters downstream from the other, the pressure difference between them is a measure of the instantaneous flow. Obviously, this still requires a central intra-arterial catheter--double-lumen, at that.

Biplanar X-ray cardiometry using radiopaque materials does work, somewhat, as a means of measuring changes in heart size, but again, this involves a catheter in place to inject the dye, and the equipment for radiography makes it hardly a convenient or portable procedure. Echocardiography is, indeed, a workable, noninvasive technique--mapping the changing volume of thoracic contents with sonar. However, significant expertise in the use of the equipment is needed, and it can scarcely be used with active, mobile subjects. One of the most common methods presently used to estimate cardiac output is the Indicator Dye Dilution method, in its various forms (varying as to the "dye" used: chemical agents with distinct colors, radioactive tracers, radiopaque materials, cold saline). Problems arise due to shunts between injection point and sampling point, from recirculation in coronary and other fast-recycle systems, from uncertainty about the mathematically most useful mode of calculation. At best, it is still an invasive technique, with arterial and venous cannulation, which still only produces a several-

beat average, and not a beat-by-beat signal.

Classically, the Fick method has been a standard for calculating cardiac output. If the individual's rate of consumption of oxygen is known, as are the arterial and mixed venous oxygen content of the blood, one can calculate the rate of blood flow by use of the principle of conservation of mass: the volume of oxygen taken up per minute, divided by the amount of oxygen taken up by a given volume of blood (the arterio-venous difference), gives the amount of blood which is taking up oxygen in that minute. The subject wears a mask connected to a calibrated spirometer, which measures the oxygen uptake, and catheters are placed to monitor mixed venous oxygen (in the right heart) and arterial oxygen (in the aorta or major peripheral artery). This principle may also be used with a number of other gaseous indicators--acetylene, for example. There are a number of obvious drawbacks: the subject is "tied down" with arterial and venous lines, and a spirometer; it measures pulmonary flow, which may be significantly different from systemic flow in a number of circumstances; it is a slow, time-average measurement, not providing beat-by-beat data, and not suited to long-term monitoring. Further, the results it yields may be greatly in error if the respiratory or circulatory conditions are changing during the duration of the measurement procedure.

To overcome some of these drawbacks, a number of researchers have modified the procedure to a less invasive version: the Indirect Fick method. It is possible, with respiratory manipulations (such as short-term rebreathing of 5-10% CO₂, or prolonging the expiratory phase of a single breath) to estimate both mixed venous and arterial pCO₂ from analysis of the expired air. Reliable and repeatable results are claimed

for this method, but several drawbacks remain: immobilization of the subject, imposition of resistive (and uncomfortable) objects in the airway, averaging nature of the determination, to name a few.

Biological Electrical Impedance Monitoring: Theory.

In the search for a non-invasive method to monitor cardiac output and other parameters of cardiac function on a beat-by-beat basis, a number of investigators have turned to monitoring the changing electrical impedance of the thorax. In 1907 Max Cremer* was able to record the beating of a frog heart by noting the changes it produced in the capacitance between two condenser plates. In 1932, Atzler and Lehman* used similar techniques and observed similar results with man. Utilizing frequencies in the 100-150 MHz range, they also noted some signal changes in phase with respiration. Work on this technique progressed relatively slowly through the 1940's and 50's, partly for lack of adequate electronics, but in the last 10-15 years both the theory and the techniques of practical measurement have become remarkably improved and compare favorably with more standard techniques.

The basic principle behind impedance cardiography derives from the relationship, for a homogenous cylindrical conductor, that the overall electrical impedance is directly proportional to the length of the cylinder, and is inversely proportional to the cross-sectional area (or varies directly as the square of the length and inversely as the total volume, since the volume is simply the length times the area).⁴³ Thus $Z = \rho \frac{L}{a} = \rho \frac{L^2}{V}$, where ρ is the volume resistivity. So stated, the situation is simple enough; the problems arise, in part, from the fact that we are not dealing with a simple, homogeneous cylindrical conductor, but with a human thorax--not cylindrical,

*Original papers in German, cited by numerous subsequent authors.

with layered skin, fat, muscle, and bone, and non-homogenous contents of lung, pulmonary vessels, heart, systemic vessels, and more. Further, problems arise from introducing electrical currents or fields into, or onto, the human body. For instance, we certainly do not want to exceed, or even approach, currents which will stimulate nerve or muscle, particularly heart muscle, so as to produce sensation or arrhythmias.⁹ The current threshold for stimulation, fortunately, rises with increasing frequency of the stimulating current, so that in the range of 50-150 KHz it is possible to use currents which provide easily measured signals without approaching the levels of neural or myocardial stimulation. Also, another problem which has been noted in practice is that at lower frequencies the capacitative reactance of the skin is the major portion of the total impedance measured, whereas this effect becomes markedly diminished at higher frequencies.^{8,14}

It is also possible to overcome some of these skin effects in a different manner. The basic technique of thoracic impedance monitoring is accomplished by applying a small current (usually through some electronic configuration which delivers, or approximates, a constant-current source) to the chest cage, and measuring the (changing) electrical potential across the thorax. Since the thoracic impedance is the ratio of potential to current, and since the current is constant, one is then effectively measuring the changing thoracic impedance. Both bipolar and tetrapolar methods have been used for this purpose; in the former, a single pair of electrodes is used to apply the current and measure the resulting potential/impedance changes, while in the latter, a different pair of electrodes monitors the changes than supplies the current. It has been repeatedly shown⁴³ that the tetrapolar technique, properly applied, eliminates much of the skin

impedance, and reduces or eliminates the effects of changes in this portion of the total impedance (as from changes in the skin--sweating, for example--or in the electrode-skin interface--drying of electrolyte, or movement of electrodes) on the impedance signal from intrathoracic phenomena.

Thus: we apply an alternating signal of about 100 kilohertz, of constant current, to the thorax, and measure the resulting potential (impedance). There are, of course, numerous ways of applying electrodes, and numerous different electrode types, but I shall not endeavor to discuss these at present. Through whatever system we use, we get some sort of signal back. It is evident from the nature of the waveform, and its timing, that the variation in impedance coincides with cardiac activity, and that there is also a slower variation coincident with respiration. If we're lucky, presuming we're interested in cardiac activity, we will have a "clean" cardiac signal, and very little respiratory component. Now all that remains is to relate the varying impedance to physiologic parameters: what is causing the varying of the signal?

There are two large problem areas remaining in impedance cardiography: delineating the specific source or sources of the signal that is monitored, and refining and justifying the mathematical methods used to translate the electrical signal into useful physiologic data. With each contraction of the heart, the ventricles empty of their content of blood, a pulse of blood flows into the pulmonary vascular tree; and a pulse of blood surges out the aorta. Various researchers^{5,10,15,26,29,35} have attributed the electrical signal to various of these sources, and no single simple explanation seems to suffice and to explain away the contrary

data. This is without a doubt the primary reason for an apparent inability to obtain, regularly, reliable, and quantitatively correct absolute values for cardiac output, but I shall discuss this in more length after review of some of the literature.

Because the source of the signal is not clear and obvious, the methods of relating it to physiologic parameters have been at least in part strictly empiric. For the study of pulse volumes in, for instance, the leg, it is easy to derive from the above equation relating volume and impedance an equation relating a change in volume (of a homogeneous cylindrical conductor) to a change in impedance: $Z_1 - Z_2 = \Delta Z = \rho L^2 \left(\frac{1}{V_1} - \frac{1}{V_2} \right) = \rho L^2 \frac{(V_2 - V_1)}{V_1 \cdot V_2} = -\rho L^2 \frac{\Delta V}{V_1 \cdot V_2}$. If ΔV is small with respect to V_1 (or V_2), we

can approximate $V_1 \cdot V_2$ by $(V_1)^2$ or $(V_2)^2$, or a "basal" measurement $(V_0)^2$: $\Delta Z \doteq -\frac{\rho L^2}{V_0^2} \Delta V$. Since we already have $V_0 = \frac{\rho L^2}{Z_0}$, we now get $\Delta Z = -\frac{Z_0^2}{\rho L^2} \Delta V$ or

$\Delta V \doteq -\rho \left(\frac{L}{Z_0} \right)^2 \Delta Z$. Nyboer has shown⁴³--for an object like a leg, with a cylindrical artery down the middle of a cylindrical leg: an electrical line (changing) in parallel with another electrical line (unchanging)--that the fixed, unchanging impedance of the unchanging tissue enters into the equation only in Z_0 , and that the volume resistivity of interest is that of the changing conductor, blood. For lack of any better version to work with, researchers have taken this equation--an approximation, for homogeneous cylinders, with simple parallel conductors--and applied it to the thorax, which is a quite different case.

The other problem is what to use for the ΔZ ? Nyboer originally proposed using planimetry to measure the area under the curve, and determine an average impedance change for each cycle; later he used the end-systolic

maximum-increasing slope of the curve (the impedance change with systole is a decrease below Z_0) to extrapolate an impedance change that would have been obtained had venous runoff not reduced it.⁴³ This has clear merit when applied to the calf, where arterial flow in diastole is zero or close to it, but the thorax works differently. Powers⁴⁸ apparently used the end-diastolic slope projected over the entire cardiac cycle, reasoning that one can measure pulse volume as well by looking at the constant outflow as by looking at the pulsatile inflow, and late diastolic slope measures the venous runoff directly. This argument suffers in the same way as Nyboer's, in the thorax. Kubicek²⁹ decided to use the early systolic maximum decreasing slope of the impedance curve, projected over the systolic ejection period, but I have been unable to find any argument for theoretical justification for this. In fact, using it, Coleman⁶ comments, "There does not appear to be a direct experimental or theoretical validation of this procedure but in our hands as well as in Kubicek's experience,.... (it) leads to reasonable values of the stroke volume...." Kinnen^{24,25} insists on a variant method which is essentially an average of Nyboer's slope method and Kubicek's, commenting, "Alternate single slope methods appear too restrictive in comparison," and citing Nyboer and Kubicek.

In any case, the majority of the papers in the recent literature follow the lead of Kubicek and his coworkers, so a further brief comment is worthwhile here. At first, their hardware was designed to give them the basal impedance, Z_0 , and a signal corresponding to the variation of the impedance, ΔZ . From the latter trace, the maximum-decreasing slope was drawn by hand, and systolic ejection timed by simultaneous phonocardiogram, so that the graphical extrapolation could be performed. Later an electronic first-derivative signal dZ/dt was produced, which had inherent timing marks

corresponding to the onset and cessation of ejection, so that the entire calculation could be made using the dZ/dt curve--the (negative) peak giving the "slope", and the timing marks the duration. Thus their working equation is $\Delta V = -R \frac{L^2}{Z_0} = \frac{dZ}{dt} \text{ min. } T_{ej}$. And this can be completely and continuously calculated electronically, if this is desired.

Impedance Monitoring: Clinical Application.

Perhaps it becomes evident from this discussion, as it certainly does from review of the literature, that impedance monitoring as a method of measuring cardiac output is a far better indicator of relative changes in output than it is of absolute magnitude. It can be highly useful if occasionally calibrated against a method which is more direct, and hence less susceptible to variations due to individual body configurations (e.g., Indirect Fick, which is also non-invasive). There is now a large volume of literature discussing the use of impedance measurements as a method of assessing cardiac output, and there follows in this paper a roughly chronologic review of the findings of a number of papers, concentrating on the last 12 years. There are also occasional reports on determination of other parameters than cardiac output, and these are also discussed.

In 1952, Bonjer⁵ reported on two series of experiments in dogs, designed to determine the source of the impedance variations which were measured on the skin. In one series either the heart or the lungs were wrapped in an electrically insulating material, in live animals, a procedure which had been found ex vivo, to eliminate electrical signals originating in the specific organ from influencing outside detectors. He showed conclusively that insulating the heart from the sensors made for a slight increase in the impedance signal, whereas insulating the lungs in like manner eliminated

the signal almost completely. While the last finding is perhaps subject to dispute, on the basis that wrapping the lungs in rubber sheeting and closing the chest effectively wraps the heart in the same sheeting, the former finding is quite significant. Indeed, since the lungs are becoming engorged with a conductor (and hence lowering their impedance) at the same time the heart is emptying of the same conductor (and hence increasing its impedance), one should logically expect the signal from the latter somewhat to "buffer" that of the former, and eliminating the cardiac signal should increase the impedance change observed. In Bonjer's second series of experiments, selected perfusion of the pulmonary or of the systemic circulation was performed mechanically in dead animals. In the latter case the impedance record recorded from the thorax was minimal, while that from the right foreleg and left hindleg was maximal; in the former, opposite findings obtained. He used a two-electrode system and a modified Wheatstone bridge detection apparatus operating at 14 KHz.

Over the past decade, Kinnen and Kubicek have been directly or indirectly responsible for the bulk of the literature on impedance cardiography. In reports in 1963^{20,21} and 1964^{22,23} they were using two-electrode systems, at first cup electrodes on the chest wall, later two metallic mesh circumferential band electrodes around the chest and neck. Much of their concern at that time was with details of proper methods of computation,²⁰ of cancellation of respiratory signal,²¹ of mapping the electric flux on the chest wall.²³ One paper discusses some comparison of impedance-determined cardiac output with oxygen consumption,²² but it has no comparison measures of actual output.

By 1965,²⁴ they had settled on a four-electrode system, using metal-mesh bands around the upper and lower neck, lower thorax at the level of the

xyphoid, and mid-abdomen. By applying a constant current at the outer pair of electrodes, the electrical flux at the inner, measuring electrodes is relatively uniform. Using a 100 KHz signal and a balance-type detector, Kinnen in 1965 determined cardiac output (using slope extrapolation rather than derivative signal) on 35 patients with cardiac disease, and compared them with either Fick or indicator dye dilution (IDD) determinations. Among patients for whom data from both Fick and IDD methods was available and correlated well, the impedance data also correlated moderately well. Poorer impedance correlation was seen in groups whose other data did not correlate well, and in those with atrial fibrillation and with atypical impedance waveforms.

Coleman et al. in two reports in 1966⁶ and 1967⁷ discussed the use of this technique to measure changes in cardiac output during heat stress. He compares Kubicek's method--using the maximum negative slope of the impedance trace, immediately after electrical systole--with that proposed earlier by Nyboer--using the maximum positive slope on the other side of this initial peak and obtains considerably better results when compared with IDD using Nyboer's method. He also notes that wetting the entire trunk with normal saline decreased the estimated cardiac output by only 6%, and did not interfere with monitoring changes when the subject sat up. In his later report, he also compared (in dogs) impedance calculations with electromagnetic flowmeter (EM) and with IDD, obtaining correlation coefficients of 0.792 between the impedance method and EM, and 0.916 between impedance and IDD.

Between 1968 and 1970 Kubicek and his co-workers, on contract to the government (NAS-9-4500)^{29,30,31,32} produced or sponsored numerous papers on a variety of aspects of the subject of impedance cardiography. An

early paper³³ was the first to describe the derivative impedance signal as a simpler way of timing and measuring the slope for determination of ΔZ . At that time they had apparently standardized on what came to be called the Minnesota Impedance Cardiograph--utilizing four band electrodes as described above, an approximately-constant-current 100 KHz oscillator, and a balance-type detector. They found that the output of their product, as an indirect electrical measurement, rather than a mechanically-coupled measurement, rendered the impedance cardiograph (ZCG) cardiac outputs more reproducible than IDD cardiac outputs. (This, of course, says nothing about accuracy and little about precision.) They also found that their ZCG determined outputs were usually higher than the corresponding IDD values, but that instituting a IDD/ZCG correction factor was a practical, useful expedient. That correction factor, however, varied from individual to individual (a phenomenon noted by nearly every investigator since). Evaluating pooled data after these correction factors had been applied, they found that 85% of the data points were within $\pm 20\%$ of the line of identity.

One particular point that apparently has never satisfactorily been resolved is the interference of respiratory signals with the cardiac signal waveform; nearly all investigators note that their ZCG output measurements were taken during breathholding.

Harley and Greenfield¹² compared ZCG records with values obtained variously by IDD and by the pressure-gradient technique. A possible source of some error for them was the use of the ΔZ -technique for calculating output, rather than the more accurate " dZ/dt times T" method developed later. They obtained moderate IDD/ZCG correlation ($r=0.68$) for 13 healthy male subjects

before and after isoproterenol infusion, while in 24 patients with heart disease the correlation between IDD and ZCG determinations was much poorer ($r=0.26$). Considerably better results were obtained when ZCG stroke volumes (beat-by-beat) in patients in atrial fibrillation were compared with similar beat-by-beat stroke volumes computed from pressure-gradient data. On the other hand, Smith et al.⁵¹ obtained excellent correlation between IDD and ZCG cardiac outputs: comparing 35 simultaneous determinations in 8 normal subjects (using dZ/dt times T), they obtained $r=0.87$ for stroke volume, and $r=0.83$ for cardiac output. After correcting individual subjects' data by the IDD/ZCG correction factor, the overall correlation was a remarkable $r=0.96$!

Some investigators have obtained relatively poor correlations between ZCG and "standard" methods. Topham,⁵⁵ in a dog study with Levophed® stress, obtained a moderately good correlation when calculating beat-by-beat output ($r=0.84$), but this improved significantly if he used an eight-beat average ($r=0.92$). In two normal human volunteers with bicycle ergometer stress, however, the eight-beat averages only yielded $r=0.84$ and 0.76 , and his scatterplots of the data show how poor a fit there was. He concludes, "It seems impractical that beat-by-beat calculation could be made in patient monitoring situations using this non-invasive method of calculating stroke volume." Others, however, have gotten results which are not quite so depressing. Bache¹ and coworkers, using the pressure-gradient technique as standard in a study of eight patients with cardiomegaly, concluded that "A linear relationship existed between the maximum impedance derivative and stroke volume which was close in some patients but was poor or varied with heart rate in others." They did not consider that the product of the maximum impedance derivative

and the ejection time predicted stroke volumes accurately. Examination of their data indicates that the impedance method can be very useful, in selected patients (although, unfortunately, there is no obvious way to select the patients ahead of time, and the way the discrepancy becomes obvious is through comparison with a standard).

William Judy and coworkers¹⁶ compared ZCG and radio-isotope IDD cardiac output determinations in normal subjects, obtaining only two data points per subject, and found a rather poor correlation ($r=0.58$) overall. Too little data was obtained to determine correlation coefficients for the individuals, but other studies suggest that they would have been better. The same researchers, noting this rather poor correlation, and the similar results of Harley and Greenfield, and noting that both comparison methods were time-average dilution techniques, decided to repeat the experiment using EM flow probe,¹⁷ whereby beat-by-beat data can be obtained, as with the ZCG. These experiments were done on 11 dogs, with the flow probe around the ascending aorta, with physiological variations induced by a variety of drug injections. In general, these results were more encouraging than their first study. Although the slope of the regression lines varied considerably for individual dogs (0.58 to 1.05), and the correlation coefficients for the individuals were also spread (0.58 to 0.98), the regression for the pooled data had a slope of 0.91, the means of the two methods were equal, and the overall correlation was remarkably good ($r=0.92$).

Another study (Steigbigel et al.)⁵⁴ utilized both IDD and pressure-gradient techniques; of 11 patients, 5 demonstrated acceptable agreement and six did not. The overall correlation was poor ($r=0.583$, with a regression line of $ZCG = 2.7 \text{ liters/min.} + 0.617 \text{ IDD}$). In using the pressure-

gradient technique, however, not only did they calculate stroke volumes (although they noted that the averaging nature of the IDD method was a possible source for discrepancy) but they also evaluated the hypothesis that the maximum of dZ/dt is a measure of the peak aortic flow rate. Their regression for stroke volume is considerably better here--ZCG = $0.08 + 0.97 \text{ PG}$ --with better correlation ($r=0.72$). The correlation between peak aortic flow and peak dZ/dt was even better ($r=0.94$).

Witsoe, Patterson, From, and Kubicek⁵⁹ reported an animal study utilizing both EM flowmeter and IDD techniques as well as ZCG, with considerable pharmacologic manipulation of the animals. Regression lines and correlation coefficients are not reported, but some comparison data are. On the scattergram plot of EM versus IDD cardiac output, 75% of the data points lie within $\pm 10\%$ of the identity line, and 96% within $\pm 20\%$. The corresponding comparisons for EM vs. ZCG and IDD vs. ZCG yield plots with approximately 70% of the data points within $\pm 20\%$ of the identity line. In speculating about the relative poor showing of the impedance method for stroke volume, they note that better correlation was seen between the flowmeter peak flow and the dZ/dt peak than was seen between stroke volumes.

Another mixed study was undertaken by Martin³⁹ using both humans with normal or depressed cardiovascular systems, and dogs, monitored by the ZCG, EM flowmeter, and IDD techniques. His overall results were not remarkably good, but individual results ranged from excellent ($r=0.91, 0.92$) through fair ($r=0.75, 0.64$) to poor ($r=0.40$) to nil ($r=0.09$). Excluding the one uncorrelated dog, the pooled data presented a correlation coefficient of 0.68, and a regression slope of 0.91. Among the humans, results were better: the worst correlation was only 0.65, and three (of 6)

subjects had r 's greater than 0.85. Here the pooled, individually-corrected data yield a correlation coefficient of 0.75.

Although the original findings which have led to "Impedance Cardiography" were determinations of variation in electrical capacitance, the great bulk of subsequent work has concentrated on resistive changes. Namon and Gollan^{40,41} have done some work to evaluate what reactive (i.e., capacitive) changes take place with the cardiac cycle. Right and left heart catheterizations were done on 14 dogs for IDD flow studies, and a variety of manipulations performed, including hemorrhage, transfusion, myocardial infarction, and hypothermia. They did not use the "Minnesota Cardiograph" since they needed to measure reactance as well as resistance, but did use a similar 4 electrode system, operating at 37 kHz. They note that the reactive cardiogram is slightly simpler in shape, with a peak slightly later in time. "In one such experiment," they comment, referring to a hemorrhage/transfusion test, "the relation between stroke volume and resistive rheometry was poor, while the correlation between stroke volume and reactive rheometry was excellent. Therefore, only reactive impedance measurements were continued." The rheogram preceded the aortic pulse during systole, suggesting it originated in the pulmonary circuit. With stroke volume varying over a 12 to 1 ratio, and cardiac output over an 8 to 1 ratio, the correlation between stroke volume and rheometry was $r=0.91$, and the standard deviation from a best-fit line was 19%. They were able to minimize respiratory artifact by utilizing spot electrodes in the midline, rather than band electrodes. Their overall excellent results suggest more should be done with this aspect of impedance monitoring.

Relatively few studies have been performed--or at least published--since the final report on Kubicek's NAS-9-4500 contract. In Japan

Hukushima et al.^{15,26} noted, using a single pair of spot electrodes placed laterally on the chest, and a constant-current 55 kHz source-- that manipulations of the pulmonary flow (occlusion, saline pumping, etc.) produced typical impedance changes. However, no study was reported of what similar manipulations of the heart or systemic circulation do to the impedance records, so their conclusion that it is the pulmonary vasculature exclusively which is monitored may be premature. Sova,⁵³ using two-electrode systems, with a variety of different electrode placements, 300 kHz current, and (apparently) bridge-type detection circuitry, obtained moderately good results on resting normals ($r=0.78$) and excellent results after a working load ($r=0.93$); similar results obtained for cardiac patients ($r=0.80$ at rest).

Lababidi³⁶ and coworkers noted in studies of children without shunts or valvular insufficiency, ZCG correlated well with Fick and IDD. When left-to-right shunts were present, ZCG grossly overestimated systemic flow but correlated almost exactly ^{with} pulmonic flow. On the other hand, however, ZCG grossly overestimated net flow in children with aortic insufficiency, suggesting it measured left ventricular stroke volume, rather than forward flow.

Some investigators have successfully extracted other data than cardiac output or stroke volume from their recordings of thoracic impedance variations. Lababidi³⁷ examined the first derivative impedance cardiogram and compared it with careful recordings of heart sounds (phonocardiograms) and with apex ballistocardiograms. He concludes that it is possible to correlate the first heart sound, and both aortic and pulmonic components of the second heart sound, as well as the atrial gallop (S_4), the ventricular gallop (S_3), and the mitral opening snap, when these latter are present. This last, called the 0 point, corresponds with the 0 point of the ballistogram, just

before the rapid filling wave.

Karnegis and Kubicek¹⁹ find consistent characteristics of the impedance waveform: a wave they label A which is "locked" to the electrocardiographic P wave, even during complete heart block, a C wave occurring during ventricular systole which is decreased in amplitude in situations (extra-systoles) which ought to decrease stroke volume, and a V wave in diastole.

More interesting still is the work of Siegel and coworkers⁵⁰ in attempting to quantify myocardial contractility using the impedance information. They find a good correlation between the time lag from electrical systole, marked by the R wave of the EKG, to the maximal rate of change of the intraventricular pressure wave (during isometric contraction), and the lag from the R wave to the (negative) peak of dZ/dt (which peak is what many use to calculate the stroke volume). The relationship is fairly linear at short times, but is fit somewhat better curvilinearly overall. Nevertheless, using a linear regression overall, the correlation is still fairly good ($r=0.88$).

Furthermore, a number of investigators (Pomerantz,^{46,47} Berman,⁴ Luepker,³⁸ Van De Water,^{56,58} Baker,² and their various coworkers) have repeatably and reliably noted that impedance monitoring equipment similar to that previously described (4 band electrodes, 100 kHz stimulating current) detects changes in intrathoracic fluid, such as pleural effusions or pulmonary edema, and have been able to quantitate the amounts. Some investigators have also commented on the relative ease with which one can obtain an EKG signal from the same set of electrodes, or--by adding a single spot electrode--monitor respiration, without interfering with the other parameters being monitored.

SUMMARY: | DISCUSSION: PROBLEMS

A survey of the literature on impedance monitoring techniques reveals both positive and negative results, both agreement and disagreement with "standard" methods. Occasionally a paper seems to show total lack of correlation, and one¹⁴ even seems to debunk the field of impedance monitoring as more a measurement of artifact, without relation to the phenomena thought to be measured, than a measurement of valid bio-impedance changes. Considering, however, that it is far easier to err enough in some aspect of the procedure--be it electrode type, electrode placement, patient condition, electronics utilized, etc.--to obscure any correlation otherwise present than it is not to do so--considering this, the mass of data collected overall in the literature is most convincing that this is, indeed, a potentially extremely useful mode of monitoring cardiac function, and, at least in a relative sense, measuring cardiac output.

Several authors^{8,11,14,44,60} discuss various aspects of the electronic and electrical methods used actually to monitor impedance. They point out that measurement systems generally fall into two categories: bridge circuits (typically a modified Kelvin double bridge, or Bagno's phase-sensitive circuit, which acts like a bridge) or constant current circuits. With the bridge circuit, of course, we must balance off the relatively large resting impedance Z_0 , and our signal of interest is the off-null output of the bridge. Unfortunately, if the basal impedance is changing, constant re-balancing is required to keep it operating near the null point, and further, the circuit becomes non-linear away from the null point. The constant --current method has the advantage of linearity, but since ohm-meter type circuits, as opposed to bridges, are exquisitely sensitive to

current changes, this has historically been difficult to achieve: either the signal source (oscillator) must operate through a very high impedance (so that any biogenic variations in impedance are small with regard to the overall impedance that it "sees") or complicated circuitry is needed with active current feedback to maintain the current source as truly constant. Hill¹⁴ points out that it is possible to obtain a truly constant current input system, rather than one approximated by utilizing very high output impedance on the driving oscillator, by using a well-designed active-feedback system. Nonetheless Gessert¹¹ maintains that "theoretically the balanced bridge is inherently superior to an ohmmeter circuit" as a means of monitoring impedance. On the other hand, Yates⁶⁰ points out that "modern operational amplifier technology makes it possible to approximate more closely a constant current source than previous designs permitted," and asserts this design is preferable because of the disadvantages of the bridge circuit mentioned above.

Pacela⁴⁴ points up another criterion for determining which circuitry to use: what, exactly do we want to measure? The impedance, and the change in impedance ΔZ , are both vector quantities, with both resistive and reactive components. The bridge circuits commonly employed measure the magnitude of the change in impedance ($|\Delta Z|$), while the constant-current circuits measure the change in the magnitude of the impedance ($\Delta|Z|$); since Z is a vector, these are, in general, not the same.

Relatively sophisticated understanding of the electronics and what they are actually measuring is required in a valid clinical study; it is not apparent that this has always, or even often, been present. There are several problem areas left in "Impedance Cardiography." On the clinical side, there have not, apparently, been adequate tests of alternate electrode configurations to the "Kubicek band system": e.g., tetrapolar

electrodes measuring from right mid-axillary line to left mid-axillary line, or from spine to sternum, or four placed along the spine, or along the sternum. Which system provides the strongest signal is one criterion, but which has least artifact is another, and which eliminates respiratory signals best is a third; further, looking laterally or postero-anteriorly ought to eliminate most aortic signals: is this good or bad? At the same time, it is necessary to determine which parameter is really the most useful: resistive changes, reactive changes, phase angle changes, magnitude of impedance changes, or change of impedance magnitude. To determine which is most useful, various ways of determining cardiac output from the electrical signal must be considered--five different methods were mentioned earlier.

This clearly multi-factorial study obviously has important non-clinical aspects to it as well: certain electronic configurations are needed to measure certain bio-electric parameters, and different ones are needed for others. If it is not clear as to the ideal circuit for certain uses, another factor is added to the study.

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<p>In the past decade noninvasive, nontraumatic methods of monitoring parameters of physiological function have been investigated with increasing interest. Of the various parameters of cardiac function, only blood pressure and the electrical activity of the myocardium have traditionally been accessible noninvasively, and only the latter in a continuous fashion. Several invasive methods exist for measurement of myocardial contractility, cardiac output, the degree of heart failure, etc., and a few for watching some of these factors noninvasively, but not, in general, non-invasively, conveniently, comfortably, and continuously. Monitoring the changing thoracic electrical impedance is a technique which satisfies all these criteria. Some of the theory of biological impedance change is discussed, and some of the drawbacks are pointed out. A survey of the literature of the last decade is presented, illustrating the fact that many investigators have consistently obtained good correlation with "standard" invasive techniques of measurement, while others have had variable results. Some of the unexplored areas in this field are discussed and directions for future research suggested.</p>			

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